REMARKS

The Office Action

Claims 1-78 are pending. Claims 1-52 and 69-78 are withdrawn from consideration as being drawn to a non-elected invention. Claims 53, 56, 59, 62, 63, and 65-68 stand rejected under 35 U.S.C. § 102(a). Claims 60, 63, and 66-68 stand rejected under 35 U.S.C. § 102(b). Claims 53, 56, 58, 59, and 61-67 stand rejected under 35 U.S.C. § 102(e). Each of these rejections is addressed in detail below.

Amendments to the claims

Claims 53, 56, and 59 have been amended to recite nucleic acids having specified structural elements in a particular 5' to 3' orientation. All of the nucleic acids recited in claim 53 feature the limitation that the positive selection marker is operably linked to regulatory elements of a host cellular gene after the nucleic acid is contacted with a cell. In claim 56, all three recited nucleic acids feature the following structural elements in a specified 5' to 3' orientation: a splice acceptor site, a negative selection marker, a positive selection marker, and a reporter gene. Both of the nucleic acids recited in claim 59 feature the limitation that the positive selection marker is operably linked to a prokaryotic promoter. Support for these amendments can be found throughout the specification, for example, at page 23, line 3 to page 25, line 2. Additional support can be found in original claims 54 and 55, which the Office has found to be allowable. Claims 54 and 55 have

been amended to an independent form, and claim 57 has been amended to include a dependency to claim 56. Claims 60 and 61 have been amended to recite the limitation that the positive and negative selection markers are operably linked to a host cellular gene after the nucleic acid is contacted with a cell. Support for these amendments can be found throughout the specification, for example, at page 6, line 27 to page 7, line 10. New claims 79 to 82 have been added to recite particular negative selection markers, positive selection makers, and reporter genes. Support for new claims 79 to 82 can be found, for example, at page 27, lines 30-31 (claim 79), page 27, line 31 to page 28, line 3 (claim 80), and page 27, lines 23-24 (claims 81-82).

Rejections under 35 U.S.C. § 102(a)

Claims 62, 63, and 65-68 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Lukacsovich et al. (WO 99/61604; hereinafter "Lukacsovich"). Claims 53, 56, 59, 62, 63, and 65-67 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Mainguy (*Nat Biotechnol.* 18:746-9, 2000; hereinafter "Mainguy"). Each of these rejections is addressed in detail below.

Lukacsovich

Claims 62, 63, and 65-68 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Lukacsovich. In applying this rejection, the Office states that Lukacsovich

discloses a gene trap vector that includes (a) a splice acceptor site and (b) a positive selection marker operably linked to a prokaryotic heat shock promoter. The Office states that Lukacsovich's vector and the cells transformed with this vector, anticipate the claims to the nucleic acids and cells (claims 62, 63, and 65-68). This rejection is overcome by the present amendments.

Claim 62 has been cancelled. With respect to rejected claim 63, that claim depends from any of claims 53, 56, 59, 60, or 61, all of which, as amended herein, recite nucleic acids that contain a negative selection marker; claim 63, directed to vectors containing a nucleic acid of these claims, also necessarily requires a negative selection marker. Lucascovich makes no mention of a negative selection marker. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F. 2d 628, 631, 2 U.S.P.Q. 1051, 1053 (Fed. Cir. 1987). Therefore, claim 63 and claims 65-67, which depend from claim 63, cannot be anticipated by Lucascovich.

Claim 68, as amended herein, features a cell that includes a first nucleic acid containing a positive selection marker, a negative selection marker, and a nucleic acid segment encoding a transactivator polypeptide; and a second nucleic acid containing a promoter operably linked to an element that is responsive to the transactivator polypeptide of the first nucleic acid. Lukacsovich fails to describe any nucleic acids containing a

negative selection marker or a transactivator polypeptide; therefore, Lucascovich does not anticipate claim 68. Accordingly, this rejection of claims 62, 63, and 65-68 should be withdrawn.

Mainguy

Claims 53, 56, 59, 62 (now cancelled), 63, and 65-67 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Mainguy. In applying this rejection, the Office states that Mainguy's description of a vector that contains, in a 5' to 3' orientation, a splice acceptor site, a reporter gene (not operably linked to a promoter), an internal ribosome entry site, a negative selection marker, a polyadenylation sequence, and a positive marker operably linked to a phosphoglycerate kinase (PGK) promoter and a polyadenylation sequence, anticipates the claimed invention. This rejection is overcome by the present amendment.

Claim 53

Amended claim 53 features nucleic acids that contain a splice acceptor site, a reporter gene, and both a positive and a negative selection marker. Each of the nucleic acids of claim 53 features a positive selection marker operably linked to a regulatory element of a host cellular gene after the nucleic acid is contacted with a cell. This important limitation distinguishes the nucleic acids of claim 53 from those disclosed in

Mainguy. Mainguy describes a positive selection marker that is operably linked to the PGK promoter. In the nucleic acid of Mainguy, the expression of the positive marker is dependent on the PGK promoter. In the nucleic acids recited in claim 53, the expression of the positive selection marker is linked to an endogenous host cell regulatory element when the nucleic acid is contacted with a cell. Because Mainguy does not teach or suggest a nucleic acid molecule having a positive selection marker operably linked to a regulatory element of a host cellular gene, Mainguy cannot anticipate claim 53.

Claim 56

Claim 56, as amended herein, features nucleic acids having, *in a specified 5' to 3' sequence*, the following structural elements: a splice acceptor site, a negative selection marker, and a positive selection marker, and a reporter gene. Mainguy does not include all of the limitations in the same arrangement as amended claim 56. The structural elements of claim 56 are recited in a specified order that is distinct from the order of elements found in Mainguy's nucleic acid. Furthermore, in each embodiment the specific order of the elements is critical to the function of that particular nucleic acid.

For example, in the first and second embodiment of claim 56, the negative and positive selection markers are immediately 3' to the splice acceptor site. Expression of the negative and positive selection markers can be inefficient and the placement of these markers immediately 3' to the splice acceptor site allows for maximal efficiency of

expression of these marker genes. In the third embodiment, the IRES is immediately 3' to the splice acceptor site and is followed by the cassette having a reporter gene and a negative selection marker. This positioning is particularly effective because the IRES allows for translation in any reading frame. The ability to generate polypeptides irrespective of the reading frame again enhances the efficiency of expression of the reporter gene and the negative selection markers. In summary, the 5' to 3' orientation of the structural elements of each of the nucleic acids specified in claim 56 confers an advantage to each of the nucleic acids. The same 5' to 3' orientation is not taught or suggested by Mainguy in any way, nor are the advantages of such an orientation suggested.

The Federal Circuit has long held that in order to anticipate a claim, "the identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). Furthermore, both the elements themselves *as well as the arrangement of the elements* must be identical to the claimed invention. "The elements must be arranged as required by the claim...." *In re Bond*, 910 F.2d 831, 15 U.S.P.Q. 1566 (Fed. Cir. 1990). Because of the differences between the arrangement of the elements of Mainguy's nucleic acid and those recited in claim 56 , Mainguy cannot be found to anticipate the claimed invention and this aspect of the rejection should be withdrawn.

Claim 59

Amended claim 59 features two nucleic acids that include all of the following structural elements *in a specified 5' to 3' orientation*: a splice acceptor site, a negative and a positive selection marker, and a reporter gene, where the positive selection marker is operably linked to a prokaryotic promoter. In both embodiments, the negative selection marker is positioned immediately 3' to the splice acceptor site. Here again, the positioning of the negative marker immediately after the splice acceptor site allows for more efficient expression of the negative selection marker. Again, the arrangement of the structural elements in the nucleic acid of Mainguy is different from the arrangement required by claim 59; therefore, Mainguy cannot anticipate claim 59 and this aspect of the rejection may now be withdrawn.

Claims 63 and 65-67

Claims 63 and 65-67 are directed to vectors and cells that include the nucleic acids of claims 53, 56, and 59. Based on the amendments of claims 53, 56, and 59 and the arguments presented above, the § 102 rejection as applied to these claims may now be withdrawn.

Rejection of claims 60, 63, and 66-68 under 35 U.S.C. § 102(b)

Claims 60, 63, and 66-68 stand rejected under 35 U.S.C. § 102(b) as being

anticipated by Brent et al. (U.S.P.N. 5,695,941; hereinafter "Brent"). In applying this rejection, the Office states that Brent teaches the claimed invention by disclosing a vector containing (1) a DNA binding domain in frame with a "bait", which the Office mistakenly characterizes as a transactivator polypeptide; (2) a reporter gene; (3) a positive selection marker (e.g., TRP1 or HIS3); and (4) a negative selection marker (e.g., URA3 gene). The Office further states that the reporter gene of Brent may be operably linked to a response element that is responsive to a transactivator polypeptide. Based on the Office's erroneous characterization of Brent's polypeptide and the present amendments, this rejection should be withdrawn.

Amended claim 60 is directed to a nucleic acid that contains a positive and negative selection marker, both of which are operably linked to a host cellular gene after the nucleic acid is contacted with the cell. The positive and negative selection markers of the nucleic acids taught by Brent are not operably linked to the promoter of a host cellular gene. Based on the absence of this limitation in Brent, claims 63 and dependent claims 66 and 67 cannot be anticipated by Brent and this rejection should be withdrawn.

Claim 68 features a cell that includes a first nucleic acid having a positive selection marker, a negative selection marker, and a nucleic acid segment encoding a transactivator polypeptide; and a second nucleic acid having a promoter operable linked to a responsive element that is responsive to the transactivator polypeptide. Claim 68 is also not anticipated by Brent because Brent does not disclose the transactivator

polypeptide that is a limitation of the claim. Applicant notes that the Office has mischaracterized the polypeptide taught by Brent as a transactivating polypeptide. Applicant directs the Office's attention to column 4, line 52, which states, "bait proteins, via their DNA binding domain, bind to their specific DNA site upstream of a reporter gene; reporter transcription is not stimulated, however, because *the bait protein lacks its own activation domain.*" (Emphasis added.) Transactivation of the reporter gene described by Brent results from the action of two individual polypeptides: one containing the bait protein and the DNA-binding domain and the other containing the activation domain and the prey protein. As Brent does not describe all of the limitations of claim 68, namely a cell having a nucleic acid sequence that includes a segment encoding a transactivator polypeptide, Brent cannot anticipate the claim. This aspect of the rejection may also be withdrawn.

Rejection of claims 53, 56, 58, 59, and 61-67 under 35 U.S.C. § 102(e)

Claims 53, 56, 58, 59, and 61-67 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Soriano et al. (U.S.P.N. 6,461,864; hereinafter "Soriano"). The Office states that Soriano describes a vector that contains a splice acceptor site, an internal ribosome entry site that controls the expression of a reporter gene (e.g., recombinase), and a positive selection marker operably linked to a prokaryotic promoter (e.g., PGK). The Office further states that this vector may also include a negative selection marker

operably linked to a promoter.

Each of the nucleic acid molecules found in claims 53 (from which claim 58 depends), 61, 63 (from which claims 64 and 65 depend), and 66 (from which claim 67 depends) contains either a negative selection marker, a positive selection marker, or both. In each of these nucleic acids, at least one of the selection markers is positioned such that its expression is controlled by regulatory elements of a host cellular gene. As the Office acknowledges on page 5 of the Office action, the positive selection marker described in Soriano is under the control of a specific promoter (e.g., PGK); therefore, the nucleic acids disclosed by Soriano do not contain all of the limitations of the claims. Thus, this rejection should be withdrawn.

Turning to claims 56 and 59, Soriano does not anticipate these claims because the structural elements of the nucleic acid of Soriano are not in *the 5' to 3' orientation* required by the claims. As described above, claim 56 features nucleic acids having, *in a specified 5' to 3' sequence*, a splice acceptor site, a negative selection marker, and a positive selection marker, and a reporter gene. The nucleic acid of Soriano does not contain the same structural elements in the same 5' to 3' orientation; therefore claim 56 is not anticipated by Soriano. Furthermore, the second and third embodiments of claim 56 feature nucleic acids having a negative selection marker operably linked to regulatory elements of a host cellular gene after the nucleic acid is contacted with a cell. Soriano does not describe a negative selection marker operably linked to the regulatory elements

of a host cellular gene. Thus, Soriano does not describe all of the limitations of claim 56 and this rejection should be withdrawn.

Similarly, claim 59 features nucleic acids that include the following structural elements *in a specified 5' to 3' orientation*: a splice acceptor site, a negative and a positive selection marker, and a reporter gene, where the positive selection marker is operably linked to a prokaryotic promoter. In both embodiments, the negative selection marker is positioned immediately 3' to the splice acceptor site. Here again, the positioning of the negative marker immediately after the splice acceptor site allows for more efficient expression of the negative selection marker. Because the arrangement of the structural elements in the nucleic acid of Soriano is different from the arrangement required by claim 59, Soriano cannot anticipate claim 59 and this rejection may now be withdrawn.

In view of the above, Applicant submits that the rejection of claims 53, 56, and 58-68 under sections 102 (a), (b), and (e) should be withdrawn.

CONCLUSION

Applicant submits that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a petition to extend the period for replying to the Office Action for three months, to and including October 8, 2004, and a check in payment of the required fee.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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